

**PLATELET INDICES IN DIABETIC NEPHROPATHY****Dr Togy Thomas Zacharia MD<sup>1</sup>, Dr Chithra Srinivasan MD<sup>2</sup>, Sreedevi CR<sup>3</sup>**<sup>1</sup>SIMATS, Thandalam, Chennai<sup>2</sup>Professor and HOD, Department of Pathology, SIMATS, Thandalam, Chennai<sup>3</sup>Associate Professor, Department of Nursing, Government Nursing college, Ernakulam**Corresponding Author: Dr Togy Thomas Zacharia MD,**

Department of Pathology, Government Medical College Thrissur, Kerala.

**Funding : self****Competing interest : none****Running title:** Platelet Indices in Diabetic nephropathy**Key words;** Platelet Indices, Mean Platelet volume, Plateletcrit, Platelet distribution width, Sysmex XN1000, Diabetic Nephropathy, Diabetes Mellites**Abstract:****Introduction:** Diabetes patients have higher platelet reactivity. Platelet Indices (PI) are advocated as biomarkers in various systemic and metabolic diseases for screening and unravelling of latent complications. **Materials and****Methods:** In the calculated sample size of 100 of which 50 T2DM patients with nephropathy (DN) and 50 T2DM patients without nephropathy (DN) was included. The PIs and biochemical parameters were examined. **Statistical****Analysis:** The platelet indices were compared between the two groups by the independent sample t test. The means of all the groups were compared using the ANOVA. **Results:.** All PIs viz AIPN, IPF, PDW, MPV, LCR,showed an increasing trend in the complications group compared to DM ( $P > 0.5$  in all cases) while PLT and PCT alone showed a decrease in the DN group. **Discussion:** The present study showed that diabetics withcomplications showed lower platelet indices, viz, PLT, MPV, P-LCR, and PCT, compared to the controls ( $P < 0.5$ ) as reported by Jiskani et al. Hekimsoy et al reported a decreased platelet count in the diabetics when comparedto healthy controls as in our study. **Conclusion:** The PCT in DN group ( $P = 0.46$  and a T of 2.02), was statistically significant when comparing the DM and DN groups. The authors observed a variation in the PIs on comparingthe DM and DN groups. All the PIs showed a increase in value in the DN group compared to the DM group ( $p > 0.5$ )

Key words: Platelet Indices (PI), Sysmex XN1000, Plateletcrit (PCT) Mean Platelet volume (MPV)

**Introduction**

Diabetes mellitus (DM), according to the World Health Organisation (WHO), is a metabolic condition with numerous aetiologies that is characterised by chronic hyperglycemia and abnormalities of protein, fat, and carbohydrate metabolism resulting from abnormalities in either insulin action or secretion, or both. India is set to be the diabetic capital of the world by 2030. Insulin resistance is the most important cause of this lifestyle disease, the modification of which can regulate onset and its complications. Nevertheless, diagnosis and management of this disease is a costly affair.



Diabetes patients have higher platelet reactivity. The use of Platelet Indices (PI) as biomarkers in various systemic and metabolic diseases for screening and unravelling of latent complications is particularly useful in Diabetes, known for microvascular complications, a consequence of antecedent endothelial activation and thrombus formation, implies a definite role for platelets, with changes specific to its size, granularity resulting in more “sticky” platelets. It is the result of both direct effects of hyperglycemia and the promotion of glycation of platelet proteins. Platelet reactivity is enhanced both by insulin resistance as well as insufficiency.

Several factors that affect platelet biology and one of them is gender. Women have larger platelet counts, and several studies have shown that this is because their increased expression of several surface receptors that enhances platelet activation<sup>1</sup>. Besides sex, age too influences the PIs in health. All the PIs but for MPV, showed a significant difference in distribution from females to males<sup>2</sup>.

Platelet activity assessments in atherothrombosis, are time-consuming, expensive, and need a large amount of sample. As an alternative, PIs viz mean Platelet Count (PC), Platelet volume (MPV), Plateletcrit (PCT), Immature Platelet Fraction (IPF), Absolute Immature Platelet Number (AIPN), and Platelet large Cell ratio (P-LCR) can be quickly assessed using common automated hemograms, on a cell counter. The data generated by CBCs usually done for other indications thus can be utilised for getting an idea of PIs.

The proliferation of literature in the last few years due to advances in cell counter technology, has argued that the change in the PIs is a testimony to the fact that “activated platelets with altered morphology and changed indices” are the culprits. Hence this study was planned to assess the PIs viz, Platelet Count(PC), Platelet Distribution width (PDW), Mean Platelet volume(MPV), Plateletcrit (PCT), Large cell Ratio(P-LCR), Immature Platelet Fraction(IPF) and Absolute Immature Platelet Number(AIPN). Diabetic nephropathy (DN) since the highest PI values were seen in this condition<sup>3</sup>. Hence the study was planned in T2DM patients, to compare the PIs in patients with and without the above complication, specifically

### **Materials and Methods**

The Institutional Ethics and Review Board had approved the study protocol (NO: IEC/GMCTSR/128/ 2021). The male T2DM patients attending Medicine and Nephrology OPD in Government Medical College Thrissur, was interviewed. Only consenting male diabetics were included in the study. The sample size was calculated to be 100 which should include 50 T2DM patients with nephropathy (DN) and 50 T2DM patients without nephropathy (DN). After obtaining the consent, samples were collected. 2 ml blood samples each in a single K3EDTA vial for HbA1c and Complete Blood count(CBC). The latter test was done after removing 20 microlitre sample for HbA1c test and thus utilizing the same sample. Further 2 ml blood each was collected in in Clot activator vacutainers for Renal function test(RFT) and in fluoride vial for Fasting blood sugar (FBS). 10 ml urine was collected for assessing the urine P/C (Protein: creatinine ratio) in the spot urine sample. The biochemical tests were done to assess and confirm the status of the patient as having or not having complication (DN). A urine P/C greater than of 30 mg/mmol (0.3 mg/mg) was considered a cutoff for diabetic patients to be classified as having DN. On the basis of history and prior treatment records, 100 consecutive patients who attended medicine OPD were included in the study after getting consent. The patients were then tested for biochemical variables mentioned and the CBC, from which PIs were derived. The CBC for PIs was done on Sysmex XN1000 (Sysmex, Kobe, Japan) cell counter in the reticulocyte mode to obtain IPF and AIPN. Care was taken to collect early morning samples before 8:00 am. The patients were seated comfortably and allowed time to relax. After that, samples were collected from right arm in EDTA vacutainers following the order of bleed. The samples particularly, CBC was estimated within

3 hours so as not to allow any storage artifacts for the platelets. Six persons had to be excluded due to other serious comorbidities. Finally the results of total, 94 consenting male diabetics were included in the study and the results analysed. The total number was divided into two groups, one with and other without complications, based on the Renal function tests. The values of the tests were entered in an excel sheet and tabulated. The quality assurance of the above mentioned cell counter was fulfilled by EQAS from CMC vellore (External Quality assurance) and the Internal Quality assurance by 3 levels of Controls, being done every day.

### **Statistical Analysis**

The biochemical parameters between the two populations were measured by Mann-Whitney U Test and the Z value. In all cases, significance was determined by  $p < 0.05$ . The platelet indices were compared between the two groups by the independent sample t test. The means of all the groups were compared using the ANOVA. Correlation was assessed by the Pearson's correlation coefficient (r) with respect to the PIs and the biochemical parameters in both DM and DN groups. Statistical analyses were performed with SPSS 28.0 software (Chicago, IL). Statistical significance was set at  $P < 0.05$ . Data were reported as mean and 95% confidence interval (CI).

### **Results**

After the division, 58 cases were of diabetic cases without complications (DM) and 40 cases were diabetic cases with complications (DN). The age in the DM group varied from 37 years to 80 years. The age in the DN group ranged from 34 to 77 years.

### **Biochemical variables**

The biochemical variables to confirm the presence of complications were, urine protein (mg), urine creatinine (mg/dl), blood urea ((mg/dl), serum creatinine (mg/dl), Glycated hemoglobin (HbA1c in %), and FBS( fasting Blood sugar in gm%). The average values were UP, UCR, B urea, S Cr, PCR, HbA1c, FBS were  $24.93 \pm 13.75$ ,  $94.45 \pm 56.21$ ,  $23.09 \pm 11.66$ ,  $1.02 \pm 0.43$ ,  $0.25 \pm 0.08$ ,  $7.56 \pm 1.62$ ,  $166.15 \pm 48.37$  respectively in DM subjects, whereas the corresponding values in DN were  $134.35 \pm 245.86$ ,  $63.39 \pm 39.82$ ,  $42.85 \pm 43.29$ ,  $2.41 \pm 3.05$ ,  $2.16 \pm 3.49$ ,  $7.59 \pm 1.94$ ,  $174.80 \pm 63.68$ . The 7 biochemical parameters that was employed in the present study, to segregate Diabetic patients with nephropathy were analyzed by Mann Whitney test and had a very significant p value. However HbA1c and FBS employed in our study was not effective in differentiating the two conditions as evidenced by the P value.

### **Platelet Indices**

On comparing the PIs between DM and DN groups, the authors observed that the PIs showed a definite difference between the two groups. All the other PIs viz AIPN, IPF, PDW, MPV, LCR, showed an increasing trend in the complications group compared to DM ( $P > 0.5$  in all cases). PLT and PCT alone showed a decrease in the DN group. The smaller PCT in DN group ( $P = 0.46$  and a T of 2.02), was statistically significant while, PLT ( $P = 0.23$ ) though smaller, did not attain significance. (Table 2). One way ANOVA carried out showed a significant difference between the means of diabetic groups and the healthy control group, as evidenced by a significant P value. (Table 3). The latter was developed by the author in the same setting and described elsewhere<sup>4</sup>. MPV did not show significant difference ( $P = 0.101$ ) between the diabetic and control groups. All PIs except MPV ( $p = 0.101$ ) implying a definite difference between the Control and the Diabetic groups considered. Compared to the healthy controls and complication group, surprisingly, the PIs were lowest in the DM group and showed an

increase in the complication (DN) group, compared to DM group. PLT and PCT differed from the rest of the PIs and showed a smaller value in DN group compared to DM group.

The Pearson correlation between the PIs and the biochemical parameters were also examined. In DM group, a significant positive correlation of UP was seen with PLT. Similarly B urea levels correlated positively with MPV, IPF. PCT showed positive correlation with PCR and FBS and a negative correlation with B urea, S creatinine. In the DN group, UP showed a positive correlation with MPV and PCT. B urea showed positive correlation with MPV, IPF and AIPN. PCT showed positive correlation with IPF and PCR. IPF showed strong positive correlation with PLT, IPF, PDW and PCT. (Table 4). The correlation B urea and AIPN (.355\*\*) turned out to be significant at 0.01 level whereas that between S cr and AIPN (.281\*), was significant 0.05 level. A similar finding between B urea and IPF (0.339\*) was also observed. A comparison was done between the HbA1c levels at a cut off of 6.5 and 7.0 for any significant association between the two groups. At a cut off of 6.5, the P value obtained was 0.785, while at a cut off of 7%, the p value was 0.1487, both of which were not significant at 0.5 and 0.1 levels.

### **Discussion:**

The present study looked at the male sex<sup>2</sup> and DN specifically for the variation in PIs. Tanima Dwivedi et al remarks that DN has the highest PIs especially MPV, PDW, PLCR, and HbA1c. Established DN had a longer diabetes duration, a higher lipid profile, FBS, HbA1c, and a statistically significant P value<sup>3</sup>, as opposed to the present study findings. Diabetes being a prothrombotic condition is characterised by poor fibrinolysis, enhanced coagulation, endothelial dysfunction, and platelet hyper reactivity. Through multiple pathways, Hyperglycemia induces platelet functional abnormalities<sup>5</sup>.

Hekimsoy et al reported a decreased platelet count in the diabetics when compared to healthy controls as in our study. Sonali et al, similar to our study, reported no significant difference in MPV between diabetics with and without complication. PDW was significantly raised in the diabetics with complication unlike our study<sup>6</sup>. PCT was the lone significant PI in our study, between two groups but this finding cannot be due to the difference in PLT, since we excluded thrombocytopenic patients from our study. Kshirsagar et al reported no significant difference in PIs among diabetes patients with and without complications. The PLT, PCT, and PDW did not differ significantly between the two groups, despite the fact that the diabetic group had much greater MPV than the controls ( $p < 0.5$ ). PLT was lower in diabetic patients with complication than in those without, similar to our study. PDW, HbA1c, and MPV were also shown to be increased in DM with complications with insignificant p value<sup>7</sup>.

A raised MPV in DM can be due to increased platelet activation, enhanced thrombopoiesis, osmotic effect or a possible shorter lifespan. Demirtas et al., Jabeen et al., Dalamaga et al. Zuberi et al., Jindal et al. Papanas et al, and Thomas et al reported a higher MPV in diabetics as was seen in our study. Studies by Silpa et al, Jindal et al. and Ashraf et al, reported higher P-LCR than healthy controls in diabetics, with values still higher in complications group ( $p > 0.5$ ), very much similar to our study ( $p = 0.244$ )<sup>8</sup>.

Interestingly ANOVA showed a higher PI in healthy controls compared to diabetic groups. As ample evidence indicates, a higher MPV value, with its diagnostic and prognostic role in disease<sup>9</sup>, was reflected in our study too, with both DM and DN group MPV exceeding the healthy control value. Contrary to this, Akinsegun et al. work revealed a reduced MPV in diabetic cases relative to controls ( $8.69 \pm 0.67$  fl in diabetics vs,  $8.91 \pm 0.80$  fl in controls.  $P > 0.5$ ). The fact that, the majority of diabetics included in the study, for varied lengths of time, were receiving treatment, including antiplatelet medicines such clopidogrel and vasoprin. which might have brought

about the decrease in MPV in our study. The irreversible inhibition of P2Y<sub>12</sub> ADP receptor by clopidogrel can impede platelet activation, hence averting an increase in mean MPV and average platelet size<sup>10</sup>.

In diabetic individuals, Özcan et al. assessed the prognostic significance of MPV, PDW, PLT, PCT, and sudden sensor neural hearing loss (SSNHL). It was noted that, those who had a complete recovery of SSNHL, had considerably higher values of platelet parameters (MPV, PDW, and PCT) than those who had a partial recovery, though the difference was insignificant implying no predictive nor prognostic value for these parameters. PLT was also shown to have no prognostic effect by Ulu et al in a 2013 study. A meta-analysis by Ji et al. showed that there was no apparent difference in the MPV values or between the cases and control groups. However Seo et al. report a predictive, but no prognostic effect of PLT<sup>11</sup>.

Veenaa et al., found a statistically significant difference between the non-diabetic and diabetic populations, with the MPVs being larger in the latter ( $P < 0.001$ ). When compared to non-diabetic participants, the median PDW levels were also larger in the diabetic population. But no significant difference in PLT was observed between healthy individuals with and those with diabetes. The studies conducted by Buch et al., Yilmaz et al., Jabeen et al., and Kodintee et al. yielded similar results<sup>12</sup>.

Unlike our study, the DM group had a higher PCT than the healthy controls, despite the fact that the platelet counts were identical in both groups as reported by Kamilla R et al, who further discovered that MPV, PCT, and PDW were higher in Diabetic patients with complications than in people without them ( $P < 0.001$ )<sup>13</sup>.

Jiskani et al very interestingly noted in their study that, Diabetics with complications showed lower platelet indices, viz, PLT, MPV, P-LCR, and PCT, compared to the controls ( $P < 0.5$ ). Only PDW showed an increase in Diabetics with and without complications compared to the healthy control population<sup>14</sup>. This finding is very similar our study wherein the PIs in the DN group showed lower values than the controls ( $p > 0.5$ ). Sherin Dib et al too established that when age increase, metformin therapy causes a greater decrease in MPV, and the reduction was statistically more substantial in older people than in younger people. It was also noted that non-diabetic controls and newly diagnosed T2DM patients had a lower MPV compared to T2IDDM patients<sup>9</sup>. MPV values were notably reduced during a 6-month metformin treatment ( $p < 0.001$ ). After six months, there was no discernible change in either the platelet count or glucose levels. MPM (Mean Platelet Mass) and HbA<sub>1c</sub> both dramatically dropped<sup>15</sup>. Findings from both the studies are similar to the present study and explains the higher MPV in controls.

According to Hekimsoy Z et al. and Kshirsagar et al., there was no discernible association between MPV and FBS, unlike our study. Sushama et al. observed a positive association between PDW and FBS, similar to our study. Unlike our study, in diabetics, Alhadas KR et al. demonstrated a favorable association between FBS and PDW, as well as between MPV and PCT and HbA<sub>1c</sub> and PDW<sup>2</sup>. Shilpi et al. examined 280 T2DM patients and an equal number of controls. They found that, in comparison to controls, diabetic patients had statistically significant p values for MPV, PDW, and P-LCR with a favourable statistical Pearson association found between HbA<sub>1c</sub>, FBS, RBS, PPBS, and complications with MPV, PDW, and P-LCR<sup>3</sup> unlike our study. In the DN group HbA<sub>1c</sub> showed a negative correlation with all other PIs except PCT which showed a positive correlation ( $p = 0.204$ ). Alhadas R et al found an association between the levels of MPV ( $p = 0.015$ ) and PDW ( $p = 0.009$ ) and HbA<sub>1c</sub><sup>7</sup>.

### **Conclusion.**

The authors observed a variation in the PIs on comparing the DM and DN groups. All the PIs showed an increase in value in the DN group compared to the DM group ( $p > 0.5$ ) while PLT and PCT ( $p < 0.5$ ) showed a decrease. The PCT in DN group ( $P = 0.46$  and a  $T$  of 2.02), was statistically significant. One way ANOVA carried out showed a significant difference between the means of diabetic groups and the healthy control group for all the PIs ( $p < 0.5$ ) except MPV ( $p > 0.5$ ). Compared to the healthy controls, the PIs were lowest in the DM group and showed a mild increase in the complication (DN) group. In Pearson correlation, PCT showed positive correlation with PCR and FBS.

**Conflict of Interest:** None

**Acknowledgement** I thank R&D department SIMATS, Thandalam, Chennai, for the support.

**Authors' Contributions** Dr Togy Thomas Zacharia was the Principal Investigator. Dr Chithra S is the PhD Guide. Mrs Sreedevi CR helped in the statistical operations in the study.

**Consent:** Obtained from willing Participants who agreed to participate in the study

**Ethical Approval:** Obtained from Institutional Ethical Committee, Government Medical College Thrissur, Kerala

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**Tables**

Table 1: Comparison of biochemical parameters in DM and DN groups.

|        | Groups     |               | z value | Mann-Whitney U Test (p value) |
|--------|------------|---------------|---------|-------------------------------|
|        | DM         | DN            |         |                               |
| UP     | 24.93±13.7 | 134.35±245.86 | 5.125   | .0001                         |
| UCR    | 94.45±56.2 | 63.39±39.82   | 3.148   | .002                          |
| B urea | 23.09±11.6 | 42.85±43.29   | 2.861   | .004                          |
| SCr    | 1.02±0.43  | 2.41±3.05     | 3.457   | .001                          |
| PCR    | 0.25±0.08  | 2.16±3.49     | 8.194   | .0001                         |
| HbA1c  | 7.56±1.62  | 7.59±1.94     | 0.091*  | 0.928#                        |
| FBS    | 166.15±48  | 174.80±63.68  | 0.718*  | 0.474#                        |

Table 2: Comparison of PIs in DM and DN groups

|           | Groups            |                   | T value | independent sample t test. (p value) |
|-----------|-------------------|-------------------|---------|--------------------------------------|
|           | DM                | DN                |         |                                      |
| Plt count | 2.20±0.75         | 2.01±0.70         | 1.197*  | .231#                                |
| AIPN      | 51745.00±57959.19 | 75444.44±98512.96 | 1.056*  | .291#                                |
| IPF       | 0.27±0.33         | 0.43±0.59         | 1.583*  | .113#                                |
| PDW       | 11.09±1.88        | 11.25±2.75        | .320    | .750                                 |
| MPV       | 9.90±0.89         | 10.06±0.87        | .872    | .386                                 |
| PCT       | 0.28±0.13         | 0.24±0.07         | 2.027   | .046                                 |
| LCR       | 24.05±25.39       | 25.39±7.08        | 1.166*  | .244#                                |

Table 3: Comparison of means between DM, DN and control groups

|           | DM                | DN                | Control group   | P value(ANOVA)      |
|-----------|-------------------|-------------------|-----------------|---------------------|
| Plt count | 2.20±0.75         | 2.01±0.70         | 2.58±0.60       | 0.0001              |
| AIPN      | 51745.00±57959.19 | 75444.44±98512.96 | 1551.49±1281.51 | 0.0001 <sup>@</sup> |
| IPF       | 0.27±0.33         | 0.43±0.59         | 0.68±0.80       | 0.0001 <sup>@</sup> |
| PDW       | 11.09±1.88        | 11.25±2.75        | 12.33±1.95      | 0.001               |
| MPV       | 9.90±0.89         | 10.06±0.87        | 10.22±0.85      | .101                |
| PCT       | 0.28±0.13         | 0.24±0.07         | 0.28±0.07       | .004                |
| LCR       | 24.05±7.25        | 25.39±7.08        | 27.12±7.00      | 0.041               |

Table 4: Pearsons' Correlation between biochemical parameters and PIs

|        | plt count | AIPN  | IPF  | PDW   | MPV   | PCT   | LCR   |
|--------|-----------|-------|------|-------|-------|-------|-------|
| UP     | .026      | .176  | .202 | .104  | .099  | .226  | .096  |
| UCR    | -.124     | .118  | .165 | .169  | .185  | .071  | .167  |
| B urea | -.171     | .122  | .045 | -.032 | .006  | -.137 | -.006 |
| SCr    | -.290     | .198  | .178 | .202  | .261  | -.089 | .268  |
| PCR    | .012      | .115  | .118 | -.050 | -.095 | .041  | -.078 |
| HbA1c  | -.047     | .181  | .183 | .115  | .127  | .052  | .120  |
| FBS    | .067      | -.017 | .003 | .049  | -.035 | .025  | -.022 |

Foot notes: Table 1: Comparison of biochemical parameters in DM and DN groups.

UP- urine Protein, U Cr- Urine creatinine, B urea- Blood urea, S Cr – Serum Creatinine, PCR – protein Creatinine ratio, Hb A1c –glycosylated Hemoglobin A1c, FBS- fasting Blood sugar.DM- diabetes mellitus without complication, DN- diabetic Nephropathy. # independent sample t test. \*t value.

Table 2: Comparison of PIs in DM and DN groups

PLT-Platelet Count, AIPN-Absolute Immature Platelet number.IPF- immature Platelet fraction.PDW-Platelet distribution width.MPV-Mean Platelet volume.PCT-Plateletcrit P-LCR- Platelet large cell ratio. DM- diabetes mellitus without complication, DN- diabetic Nephropathy. # Mann-Whitney U Test \*z value



Table 3: Comparison of means between DM, DN and Control groups

DM- diabetes mellitus without complication, DN- diabetic Nephropathy. @ Kruskal-Wallis test

Table 4: Pearsons' Correlation between biochemical parameters and PIs in DM group

DM- diabetes mellitus without complication, UP- urine Protein, U Cr- Urine creatinine, B urea- Blood urea, S Cr – Serum Creatinine, PCR – protein Creatinine ratio, Hb A1c –glycosylated Hemoglobin A1c, FBS- fasting Blood sugar. DM- diabetes mellitus without complication, DN- diabetic Nephropathy. PLT-Platelet Count, AIPN- Absolute Immature Platelet number. IPF- immature Platelet fraction. PDW-Platelet distribution width. MPV-Mean Platelet volume. PCT-Plateletcrit P-LCR- Platelet large cell ratio. DM- diabetes mellitus without complication, DN- diabetic Nephropathy.

\*Correlation is significant at the 0.05 level (2-tailed).

\*\* Correlation is significant at the 0.01 level (2-tailed).